

Development of IgA Nephropathy after Clinical Remission of Dense Deposit Disease

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Dense deposit disease (DDD) is a rare primary glomerulonephritis characterized by continuous band-like intramembranous dense deposits detectable on electron microscopy. We describe a case of DDD with sequential mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, minor glomerular alterations, and a second round of mesangial proliferative glomerulonephritis during a 13-year period. Electron dense deposits were typical of DDD in the first and second biopsies taken one year apart. However, deposits dissolved and the glomerular cellularity and basement membrane normalized with clinical remission, which was achieved by a course of immunosuppressive therapy lasting seven years. The fourth biopsy was performed due to recurrence of microscopic hematuria and showed predominant mesangial IgA deposits without glomerular capillary alteration, which was interpreted as development of IgA nephropathy after remission of DDD or coexistence with nearly healed DDD in this patient.

Key Words : Hypocomplementemic glomerulonephritis, Dense deposit disease, IgA nephropathy

INTRODUCTION

Dense deposit disease (DDD) is a rare primary glomerulonephritis also known as membranoproliferative glomerulonephritis (MPGN) type II. As opposed to the typical light microscopic features of MPGN, DDD

includes a wide spectrum of glomerular alterations^{1, 2)} and sometimes simulates other primary glomerulonephritides. Deposits of C3 alone along the glomerular peripheral capillary wall and continuous band-like intramembranous electron-dense deposits are both diagnostic features of DDD, regardless of glomerular histology^{3, 4)}.

We followed a case of DDD that displayed diverse morphologic, immunohistologic, and electron microscopic features over a 13-year period. The patient underwent four renal biopsies that showed, sequentially, mesangial proliferative glomerulonephritis, MPGN,

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minor glomerular changes, and a second round of mesangial proliferative glomerulonephritis. The fourth biopsy taken three years after clinical remission showed predominant mesangial IgA deposits. Since IgA deposits are not typical in DDD, we believe that IgA nephropathy developed after remission of DDD, or that both diseases coexisted in this patient.

CASE REPORT: CLINICAL SUMMARY

A 3-year-old boy presented with gross hematuria, hypocomplementemia, and an elevated anti-streptolysin O (ASO) titer in May 1993. He had no history of previous renal disease. His family history and physical examination were unremarkable. Laboratory results included: hemoglobin, 9.0 g/dL; blood urea nitrogen, 6.0 mg/dL (normal: 5–25 mg/dL); creatinine, 0.3 mg/dL (normal: 0.5–1.2 mg/dL); ASO titer, 680 Todd Units (normal: <200 Todd Units); C3, 5 mg/dL (normal: 90–180 mg/dL); and C4, 35 mg/dL (normal: 10–40 mg/dL). Urinalysis showed 1+ proteinuria and many red blood cells (RBCs), but nephrotic features were not observed. He was treated with penicillin V and discharged. His ASO titer dropped to 200 Todd Units, but mild hematuria, proteinuria, and hypocomplementemia persisted. In August 1993, the first renal biopsy was performed.

In September 1994 (4-year-old), a second renal biopsy was performed due to persistent hypocomple-

mentemia and urinary abnormalities. Treatment with prednisolone and azathioprine was started after the biopsy and continued until May 1996, at which time treatment was switched to deflazacort, azathioprine, and cilazapril. Hematuria and proteinuria resolved 5 months after the initiation of prednisolone and azathioprine therapies, but serum complement levels did not normalize until November 2001 (11-year-old). Medication was discontinued in July 2002.

In January 2003 (13-year-old), serum C3 level was normalized for the first time to 125 mg/dL, and urinalysis revealed 0–2 RBCs/HPF. A third biopsy was performed to assess the therapeutic effect of steroids and azathioprine on renal pathology 10 years after the second biopsy.

In January 2006 (16-year-old), gross hematuria reappeared. Urinalysis revealed 5–10 RBCs/HPF and 1+ proteinuria. C3 level was 112 mg/dL and C4 level was 17.8 mg/dL. Serum IgA was 279 mg/dL (normal: 70–400 mg/dL). The fourth renal biopsy was performed.

CASE : PATHOLOGICAL FINDINGS

The first renal biopsy contained 53 glomeruli, most with severe and global mesangial expansion with mesangial cell proliferation (Fig. 1A). A few neutrophils were present in the capillary lumen. Glomerular basement membranes were focally and segmentally

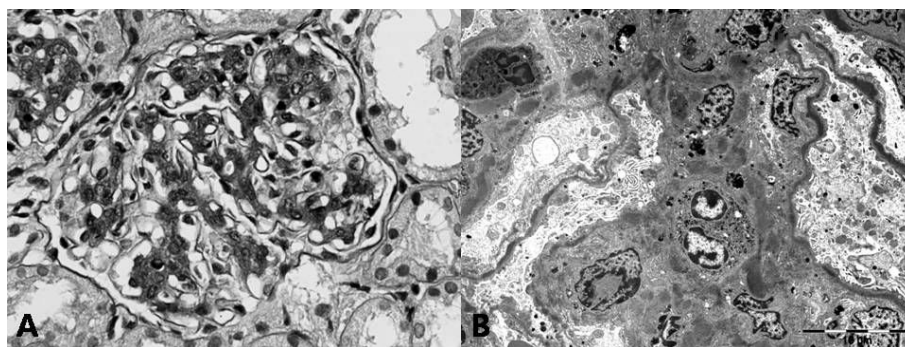


Fig. 1. The first renal biopsy demonstrated global mesangial expansion and severe mesangial proliferation (A, PAS, ×400). Electron microscopy demonstrated continuous intramembranous deposits (B).

thickened with a double-contour feature on methenamine-silver stain. The tubulointerstitium and blood vessels were unremarkable. Immunofluorescence revealed C3 (+) and fibrinogen (+/-) deposits in the mesangium and along the capillary walls. Electron microscopic examination showed severe mesangial expansion with mesangial proliferation and several nodular electron dense deposits. Glomerular capillary lumina were focally occluded and contained neutrophils. Glomerular basement membranes were markedly thickened and had several subendothelial and subepithelial deposits in addition to continuous intramembranous deposits (Fig. 1B).

The second biopsy contained 76 glomeruli, almost all with diffuse severe mesangial cell proliferation. Glomerular basement membranes were diffusely thickened with a chain-like appearance and showed a focal double-contour feature on methenamine-silver stain (Fig. 2A). The tubulointerstitium and blood vessels were unremarkable. Immunofluorescence revealed C3 (+++), fibrinogen (++), and IgM (+/-) deposits both along the capillary walls and in the mesangium. Electron microscopic examination showed severe mesangial expansion with mesangial proliferation and many electron dense deposits (Fig. 2B). Glomerular capillary lumina were partly occluded by swollen endothelial cells. Electron dense deposits were similar in location and amount to that of the first

biopsy and also had areas of resolution. The glomerular epithelial foot processes were diffusely effaced. A linked-sausage appearance of electron dense deposits was present along the tubular basement membrane.

The third biopsy specimen showed a small core of renal cortex including four glomeruli. The glomeruli appeared intact except for focal mild mesangial proliferation. No alteration was observed in the tubulointerstitium or blood vessels. On immunofluorescence microscopy, there were granular mesangial C3 (+/-), IgM (+/-), and fibrinogen (+/-) deposits. Electron microscopic examination showed a relatively even glomerular basement membrane without electron dense deposits. The mesangium contained a few electron dense deposits. Electron dense deposits persisted along the tubular basement membrane.

A fourth biopsy contained 19 glomeruli showing focal, segmental, mild mesangial expansion and mesangial proliferation (Fig. 3A). The glomerular capillary loops of one glomerulus showed adhesion to Bowman's capsule and fibrous crescent. The glomerular basement membrane was not thickened. The tubules and interstitium were well-preserved. Immunofluorescence sections demonstrated granular deposits of IgA (++), C3 (+), and fibrinogen (specks) in the mesangium (Fig. 3B). On electron microscopy, the glomerular basement membrane was relatively

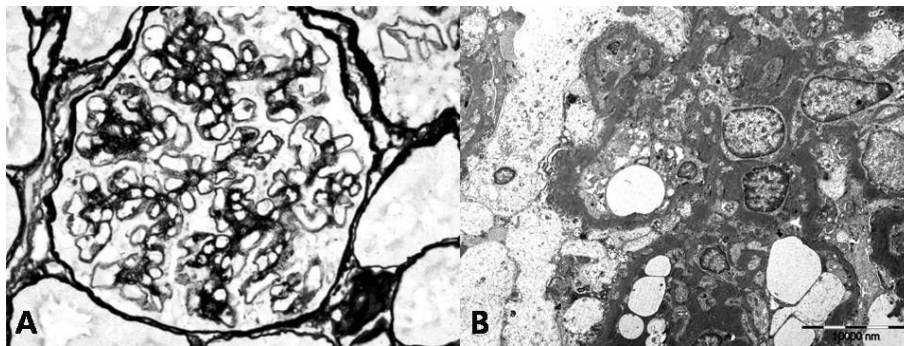


Fig. 2. The second biopsy demonstrated mesangial proliferation and thickening of the capillary walls with focal double-contour on methenamine-silver stain (A, $\times 400$). Electron microscopic examination showed mesangial expansion with many electron dense deposits (B).

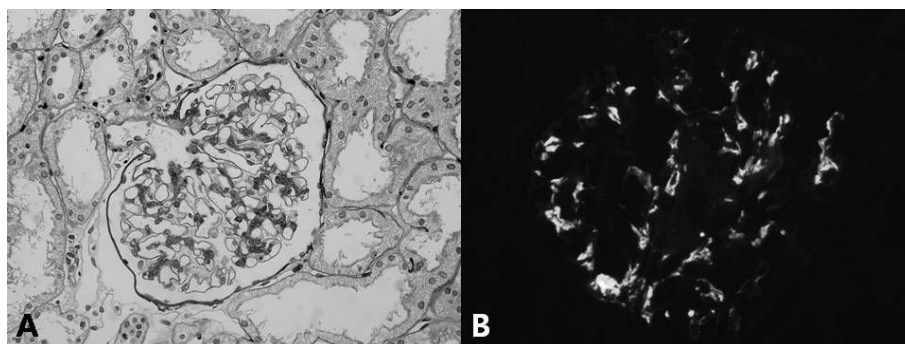


Fig. 3. The forth biopsy demonstrated mild mesangial expansion and proliferation (A, PAS, $\times 400$). Mesangial IgA deposits were identified by immunofluorescence microscopy (B, $\times 400$).

Table 1. Summary of the Clinical Courses and Pathological Findings

Biopsy	1st (3-year-old)	2nd (4-year-old)	3rd (13-year-old)	4th (16-year-old)
Proteinuria	1+	1+	–	1+
Random urine RBCs (0–5/HPF)	Many	3–5	–	Many
C3 (90–180 mg/dL)	5	22	125	112
ASO titer (<200 Todd U)	680	280	241	Not checked
LM	Mesangioproliferative	Membranoproliferative	Minor change	Mesangioproliferative
IF	C3 (1+, Mes, Cap)	C3 (1+, Mes, Cap)	C3 (+/–)	IgA (2+, Mes), C3 (1+, Mes)
EM	IM, SEn, SEp	IM, SEn, SEp	Mes (trace)	Mes
Treatment	Penicillin V	Prednisolone, Azathioprine	No medication	Enalapril

Abbreviations : ASO, anti-streptolysin O; C, complement; Cap, capillary; EM, electromicroscopy; IF, immunofluorescence; Ig, immunoglobulin; IM, intramembranous; LM, light microscopy; Mes, mesangial; RBCs; red blood cells; SEn, subendothelial; Sep, Subepithelial

even and of normal thickness. The epithelial foot processes were well preserved. The mesangium was focally expanded by cellular and matrix increases and contained massive paramesangial electron dense deposits. Nodular electron dense deposits were also present focally along Bowman's capsule and trace amount of intramembranous dense deposits were present along the glomerular basement membrane. The diagnosis of IgA nephropathy, subclass III, according to the Haas classification, was made⁵⁾. Three years after discharge, microscopic hematuria persisted.

The clinical courses and pathological findings are summarized in Table 1.

DISCUSSION

DDD is a rare primary glomerulonephritis that affects mostly between the ages of 5 and 15 yr and the overall long-term prognosis is poor⁶⁾. Spontaneous remission is rare and progression to chronic kidney disease develops at least 50% of patients within 10 years⁶⁾. We have observed our patient for 13 years and the clinical course was milder than usual in that near complete remission of symptoms was obtained. We observed decreased serum C3 level in our patient, which is a typical finding of DDD. Recently, CH50, C3d, C3 nephritic factor (C3NeF), factor H and other autoantibodies as well as C3 and C4 were proposed

as important serologic markers diagnosing DDD⁶⁾. In our patient, only C3 and C4 could be checked.

The pathologic findings of DDD is characterized by continuous band-like intramembranous dense deposits on electron microscopy^{3, 4)}. Light microscopic features are diverse^{4, 7)} and the mesangial proliferative pattern is the most common of all histologic variants⁷⁾. Our case demonstrated diverse features of mesangial proliferative change, membranoproliferative change, minor glomerular alterations and mesangial IgA deposits, sequentially. Subepithelial and subendothelial electron dense deposits were observed along with intramembranous deposits. These deposits were associated with mesangial proliferation and interposition, but dissolution of these deposits and loss of lamina densa duplication were also observed in follow-up biopsies.

Several reports suggest that DDD demonstrates diverse histologic features. For example, endocapillary proliferation has been reported as an early histologic feature of recurrence after transplantation⁸⁾. In porcine models of MPGN, mesangial hypercellularity precedes mesangial interposition into peripheral capillary loops, increasing in degree along with disease progression⁹⁾. Some authors report the histologic improvement of DDD by an alternate-day prednisone regimen^{10, 11)}. A recently suggested treatment option including plasma infusion or exchange, rituximab, sulodexide, and eculizumab¹²⁾ may also accompany histologic improvement. According to these reports, the sequential histologic changes observed in our case can be explained in relationship to disease progression or therapeutic response.

The morphologic diversity of DDD can make it difficult to differentiate from other glomerulonephritides. In our case, poststreptococcal glomerulonephritis and MPGN type III were the most important differential diagnoses. Acute poststreptococcal glomerulonephritis^{7, 8)} was suspected in our case at initial presentation due to the patient's fever and elevated ASO titer. Presentation with acute nephritic syndrome and C3

deposits along the capillary loops are frequently observed both in DDD and poststreptococcal glomerulonephritis. The conditions can be differentiated by the fact that co-deposits of the other immunoglobulins are frequent in poststreptococcal glomerulonephritis, but continuous intramembranous deposits are not. Intramembranous electron dense deposits may be seen in the Anders and Strife variant of MPGN type III, but breaks and lamellations in the intervening lamina densa are frequently associated with these deposits¹³⁾. Persistent C3 deposits regardless of morphologic transformation and areas of continuous intramembranous deposits along the lamina densa also favored a diagnosis of DDD.

The patient showed features of IgA nephropathy in the fourth biopsy after clinical and histologic remission of DDD. Mesangial deposits were massive and predominantly composed of IgA. Although DDD is not an immune complex-mediated disease, glomerular co-deposits of immunoglobulins can be observed in DDD patients during follow-up. Joh et al.²⁾ reported IgG, IgA, and IgM deposits along the peripheral capillary walls in six, three, and nine of ten DDD cases, respectively. IgA deposits, which were focal and segmental in two cases and intense in one case, were present along the peripheral capillary wall without mesangial staining. Katz and Chan¹⁴⁾ reported a case of IgA nephropathy with irregular intramembranous dense deposits. The case showed IgA and C3 deposits both along the glomerular capillary walls and in the mesangium, but mesangial staining of IgA was not intense as in typical IgA nephropathy. Our case is different from these cases in that IgA deposits were intense and localized in the mesangium without peripheral capillary deposits. These morphological findings in the fourth biopsy favored de novo development of IgA nephropathy. However, considering the presence of weak intramembranous deposits, the mesangial deposits could be combined immune-type deposits of IgA nephropathy and residual deposits of DDD after healing in the glomerular basement membrane. He has

been treated with enalapril since the diagnosis of IgA nephropathy. Urinalysis at the last follow up in January 2009 showed no proteinuria and 3–5 RBCs/HPF. The blood urea nitrogen level was 10.1 mg/dL, the serum creatinine level was 0.9 mg/dL and other laboratory findings were also within normal range. Features of partial lipodystrophy or development of ocular drusen that can accompany DDD were not shown. Reports of more cases similar to this unusual case would be helpful in understanding the pathogenesis and clinical course of these overlapping conditions.

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